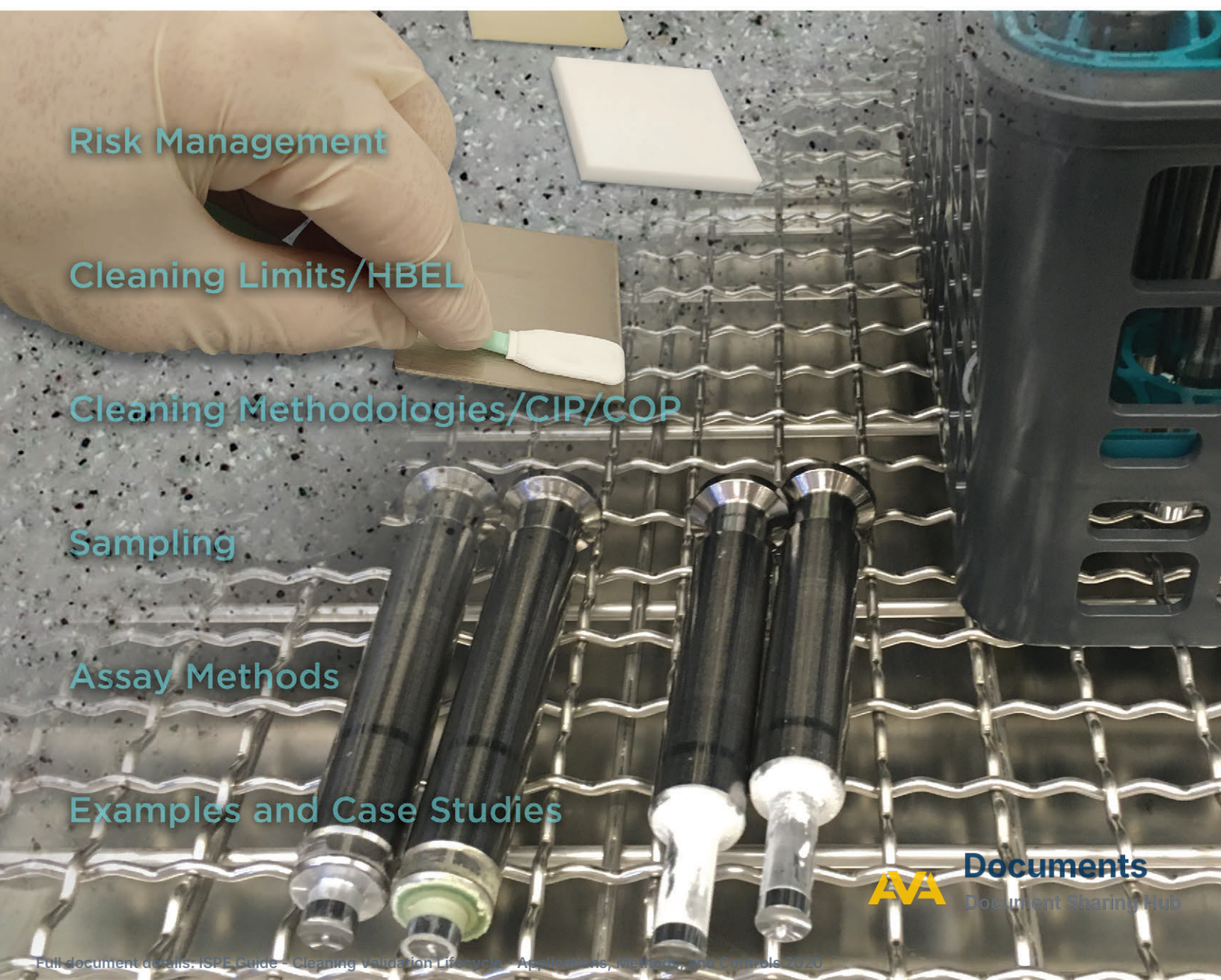


Cleaning Validation Lifecycle – Applications, Methods, and Controls



Risk Management

Cleaning Limits/HBEL

Cleaning Methodologies/CIP/COP

Sampling

Assay Methods

Examples and Case Studies

Cleaning Validation Lifecycle – Applications, Methods, and Controls

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Preface

Regulatory agencies expect the development and validation of a compliant cleaning program. This critical activity ensures that the risks of contamination, product carryover, and cross-contamination are controlled, minimized, and monitored to safeguard patient safety and product quality.

This *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls* describes the application of the process lifecycle model to cleaning. This will aid organizations in developing and adopting scientifically sound approaches, resulting in a robust cleaning validation program.

An integral part of an effective cleaning program is using risk-based approaches in the design and management of the validation process; accordingly, this ISPE Guide is aligned with the principles described in the *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products [Risk-MaPP] (Second Edition)*.

This *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls* promotes the use of health-based exposure limits (HBEL) and offers guidance and examples for developing and/or transitioning to the determination of cleaning specifications using HBEL.

Created by a team of industry experts with global experience, this ISPE Guide is intended as a reference for the cleaning lifecycle model as well as a practical guide for applying the theory and concepts to help create compliant and effective cleaning programs.

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1 Introduction

Cleaning validation is a requirement of the biotechnology, biological, pharmaceutical, diagnostics, medical device, nutraceutical, and in some cases cosmetic industries. Regulatory agencies expect the development and validation of a compliant cleaning program. This critical activity ensures that the risks of contamination, product carryover, and cross-contamination are controlled, minimized, and monitored to safeguard patient safety and product quality.

An effective cleaning program shall be in place to provide documented evidence that cleaning processes will reproducibly remove previous product or other residues on product contact equipment surfaces below scientifically set acceptable levels [1]. Cleaning soiled surfaces allows the use of that equipment with other products or materials without undue risk of cross-contamination of those products or materials.

This *ISPE Guide: Cleaning Validation Lifecycle – Applications, Methods, and Controls* aims to provide a comprehensive explanation and hands-on guidance for cleaning validation lifecycle. It describes the fundamental elements applicable to the pharmaceutical, biotechnology, and other life science-related industries. This ISPE Guide has been created as a consensus document by a team of industry experts after careful consideration of regulatory requirements, industry practices, and feedback received during peer review. Alternate approaches to the ones described here to meet regulatory requirements may be acceptable if scientifically justified and properly documented. A country, company, or facility may have additional or unique requirements that could necessitate adaptation of the principles presented in this ISPE Guide on a case-by-case basis.

1.1 Background

The main purpose of cleaning validation is to prove the effectiveness and reproducibility of the cleaning process for a given piece of production equipment to prevent cross-contamination and adulteration of a Drug Product (DP), substance, or biological product from other active ingredients, chemicals, and other unintended compounds or microbiological contamination. It also establishes criteria to reduce patient risk by producing a safe and effective product.

Cleaning validation is labor intensive, requiring resources from multiple areas. Functions involved in cleaning activities include:

- Research and Development (e.g., establishment of manufacturing processes and corresponding cleaning agents)
- Process Development (e.g., establishment of cycle development studies, calculations)
- Toxicology (to determine Health-Based Exposure Limits (HBELs) and provide Acceptable Daily Exposure (ADE)/ Permitted Daily Exposure (PDE) information as needed)
- Virology (when cleaning biologicals and equipment used for advanced therapies)
- Engineering (for equipment design and readiness)
- Production (e.g., operating equipment, supporting validation execution, troubleshooting failures)
- Validation (e.g., writing validation protocols, reports, and master plans, and/or executing validation protocols)
- Quality Control (e.g., sampling, laboratory recovery studies, methods development, and validation studies)
- Quality Assurance (e.g., ensure compliance with GMP regulations)

Over the years regulated GxP industries have acknowledged that cleaning validation is an integral part of manufacturing operations and should be treated as a critical process. Applying a process lifecycle model to cleaning processes helps ensure the application of scientifically sound approaches, resulting in a robust cleaning validation program.

1.2 Purpose and Objectives

1.2.1 Benefit

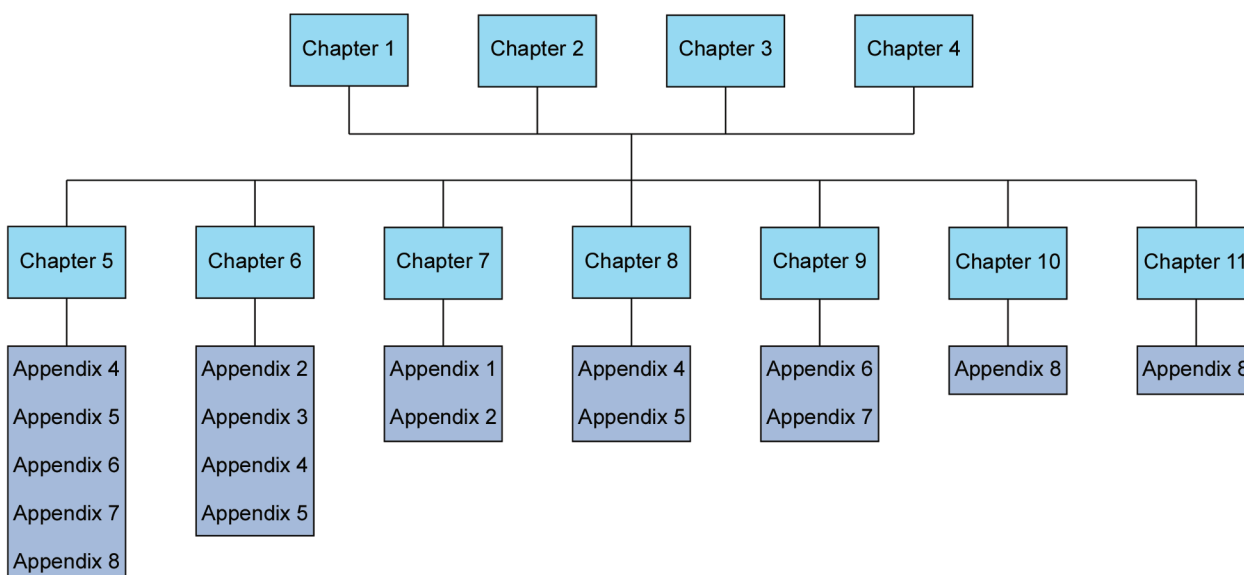
This Guide provides a hands-on approach to support the pharmaceutical, biotechnology, and other life science industries in the development and establishment of compliant cleaning programs that will meet or exceed regulatory expectations. This Guide is intended as a reference for the cleaning lifecycle model and a practical guide for applying the theory and concepts to product contact surfaces to help create compliant and practical cleaning programs.

1.2.2 Scope

Application of phased appropriate GMPs for commercial and clinical manufacturing cleaning practices (validation or verification) is addressed in this Guide.

As illustrated in Figure 1.1, this Guide is designed in three parts. Chapters 1 to 4 provide an overview, containing industry trends, regulatory references, cleaning risk management, and the cleaning validation lifecycle. The reader is then led through the validation lifecycle stages. Chapters 5 to 11 present in-depth information on planning the process, preparing and conducting validation, and implementing and maintaining the validated processes. These chapters provide guidance for creating new programs as well as bringing legacy programs in line with current regulatory expectations. This information culminates into several examples and case studies (Appendices 1 to 8) to help increase the reader's understanding of the application of these principles in the cleaning process.

Figure 1.1: Guide Structure

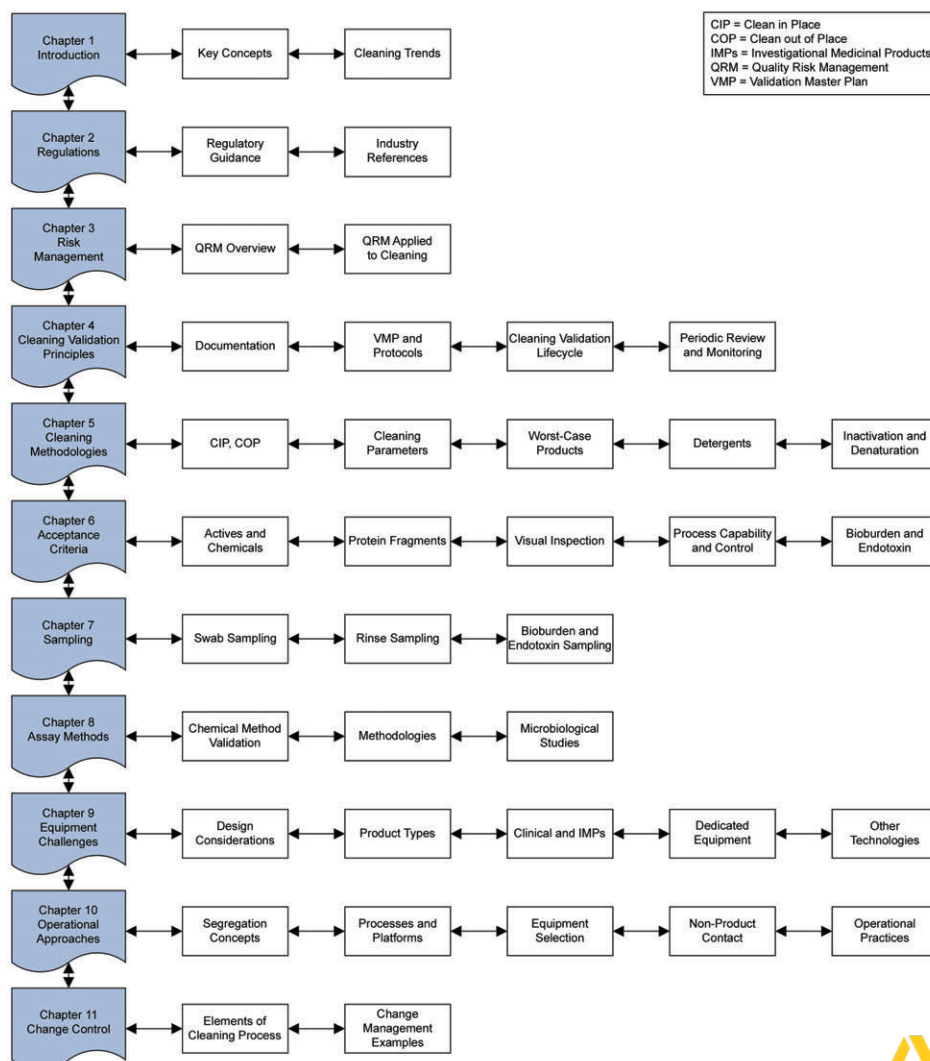


The Guide discusses the following topics (see also Figure 1.2):

- Current regulations and relevant standards
- Application of risk management in cleaning validation
- Description of the cleaning validation lifecycle model

- Cleaning methodologies
- Creation of cleaning validation acceptance criteria
- Determination of visual inspection limits
- Cleaning validation strategies
- Documentation for cleaning validation programs
- Calculation and justification of residue limits
- Validation of testing and sampling methods
- Periodic review and revalidation
- Equipment issues and challenges
- Examples and case studies

Figure 1.2: Chapter Organization of this Guide



This Guide pertains to pharmaceutical, biotechnology, and other life science industries with the exception of medical devices. Cleaning validation requirements for medical devices are contained in ASTM F3127 – 16, Standard Guide for Validating Cleaning Processes Used During the Manufacture of Medical Devices [2].

Also excluded from this Guide are clean rooms cleaning and controls, and facility cleaning and disinfection.

A short discussion on indirect and non-product contact surfaces is in Section 10.4; however, they are not within the scope of this Guide. See the *ISPE Baseline® Guide: Volume 7 – Risk-Based Manufacture of Pharmaceutical Products [Risk-MaPP] (Second Edition)* [3] for developing control strategies to prevent cross-contamination of any surface.

1.3 Key Concepts

Cleaning validation, according to Eudralex Volume 4, Annex 15: Qualification and Validation [4] is:

“Documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.”

Risk-based approaches are an integral part of cleaning validation. The evaluation of hazards, the analysis of risks, and the mitigation of those risks with control measures using risk management principles are described in Chapter 3.

A process validation lifecycle model (US FDA Guidance for Industry: Process Validation [5], EMA Guideline on process validation for finished products – information and data to be provided in regulatory submissions [6]) can be applied to cleaning processes. Chapter 4 of this ISPE Guide explains the adaptation of a lifecycle model to cleaning validation.

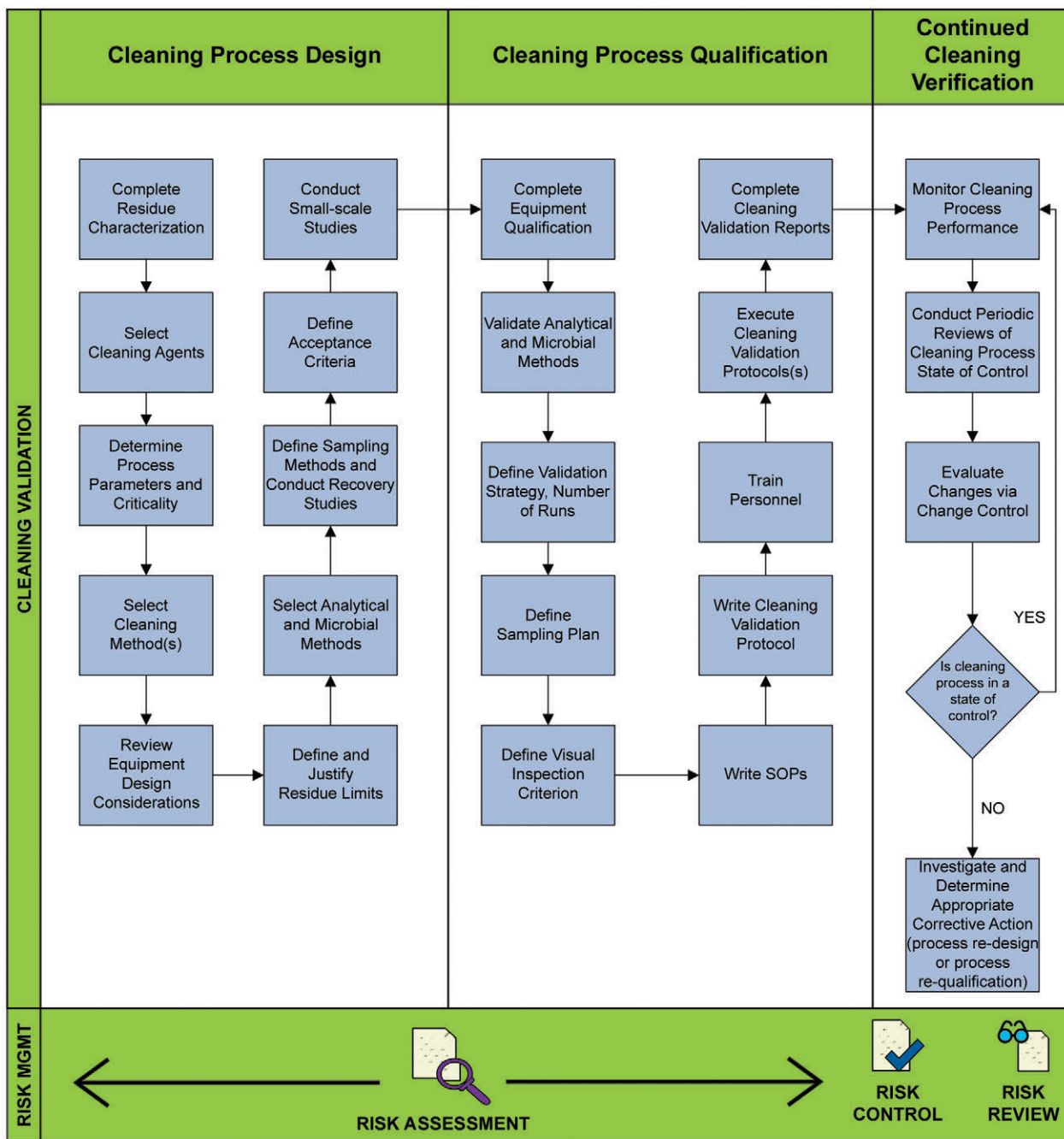
Cleaning validation strategies include the practice of justifying the grouping of equipment with the same design. Validating the cleaning method for multiple units of the same design can be simplified by selecting representative units for validation and an appropriate sampling plan following a science and risk-based approach. Similarly, validating a cleaning method using a minimum number of runs representing a combination of conditions with justification of the bracketing of parameters (e.g., size, volume, concentration) can also reduce the validation effort. Section 5.6 describes these practices in more detail.

The establishment of HBEL is the dominant approach for safety cleaning limits. When calculating the cleaning threshold values, the terms PDE, ADE, and HBEL are used interchangeably in this Guide.

Cleaning validation is not required for the manufacturing of clinical batches; cleaning verification is acceptable. Sometimes cleaning validation may not be practical, such as for infrequent batch runs; however, cleaning verification must be used until a process is validated. Refer to Section 9.7 for cleaning verification practices.

Figure 1.3 presents a roadmap to conduct cleaning validation, from process design to process qualification and continued process verification. This Guide provides help on how to approach each step of the cleaning process validation roadmap. Risk-based approaches are an integral part of the cleaning validation effort, and are also illustrated on the diagram, spanning from risk assessment to risk control and risk review.

Figure 1.3: Cleaning Process Validation Road Map



1.3.1 Current Considerations and Trends

Cleaning validation has been performed for several decades in the regulated industry. Despite the different approaches used to achieve cleanliness requirements, there are common areas that represent challenges for some manufacturers and should be taken into consideration when developing a comprehensive cleaning program.

Health-Based Exposure Limits (HBEL) – The establishment of cleaning limits using a HBEL approach is the recommended guidance for setting safe residue limits (see EMA [7]). However, there are several situations where alternate approaches for scientifically based limits are required. For example, actives manufactured from biological processes are usually inactivated, denatured, or degraded when strong cleaning processes are used. An appropriate HBEL may not be available to describe the safety risks of the resulting fragments or degradation products.¹ In addition, development of an Investigational Medicinal Product (IMP), or during early clinical batch production, may lack HBEL-specific information. Furthermore, legacy facilities may not use HBELs as part of their cleaning programs. The transition from traditional approaches to a HBEL-based cleaning program needs to be achieved. Refer to Sections 6.1.1.3 and 6.1.5 for guidance on how to transition from a legacy residue limit to a HBEL-based limit. See also Chapter 6 for additional guidance on how to justify limits for cleaning validation.

Corrosion Management – The corrosion of metal surfaces may reach a point where the established cleaning process is affected. Corrosion may also affect the formation of biofilms, as an increase in roughness may reduce the cleanability of the surface and promote biofilm formation. Each company should have a system to manage metal corrosion (e.g., rouge issues). Corrosion levels that can affect the performance of the validated cleaning process are those that release metal particles into the process, change the color of the rinse/swab samples, cause a failure of visual inspection, or change the equipment surface characteristics making it harder to clean. Monitoring vessel product contact surfaces and using visual inspection criteria to identify corrosion on surfaces should be part of the controls to manage this issue. Other preventive measures (e.g., periodic passivation or chemical treatments) should be considered for corrosion prone or critical equipment.

Furthermore, plastic surfaces may be impacted by chemical attack causing cleaning surface degradation, and glass surfaces may be subject to oxidative attack and delamination. Similar controls to the ones in place for corrosion management should be applied where necessary to ensure consistent and effective cleaning.

Manual Cleaning Processes – The reproducibility of manual cleaning processes represents a challenge to validate due to the variability of manual steps. Manual processes should be described in detail and designed in a robust way to ensure that the cleaning objectives are reached despite the variability in application. Operators should be trained and periodically assessed to prevent drifting of manual cleaning techniques or skills that may impact the final residue levels. Approaches such as alternating cleaning agents, extended cleaning times, or increased concentration of cleaning agents should be considered during the development of the cleaning process to improve process robustness. The reproducibility required for manual cleaning is more achievable with higher PDE/ADE products than with lower ones. It may not be possible to validate manual cleaning processes at the levels required for low PDE/ADE products, or at least extensive (and potentially prohibitive) work may be required. As such, consideration should be given to automated cleaning to allow greater consistency, or to dedicated equipment for these products. Refer to Appendix 6 for an example of parameter setting for manual cleaning procedures.

Buildup of Biological Residues – Clean in Place (CIP) systems may require occasional manual scrubbing of surfaces or the use of alternate cleaning agents to remove residues deposited from some biological processes. If left unattended, the residues may accumulate and affect the cleaning performance. Users should assess the risk of biological residue removal techniques and consider the formation of persistent residue deposits during cleaning process development, and ensure the process and frequency of residue removal is properly documented. Appropriate visual inspection criteria to determine the presence of biological residues should be included in the cleaning procedures of equipment impacted by these types of residues. Enzymatic degradation or manual cleaning steps should be considered in the cleaning process procedure [8].

Formation of Biofilm – Biofilms can be a persistent problem in GMP water systems, facilities, and some processes based on continuous manufacturing. Biofilm is the accumulation of microbial cells to a surface forming a film or layer of extracellular material. Prevention of biofilms, as well as their formation and removal from equipment surfaces, need to be considered during cleaning process development. Biocides and other sanitizing agents are used to prevent biofilm formation.

¹ ISPE Baseline® Guide: Risk-MaPP (Second Edition) [3] describes the approach of treating any degradation fragment as the product itself unless there is additional toxicological information to show differently.

Air/Liquid Interface in Vessels – Many processes leave residues at the air/liquid interface of vessels. If these residues are not removed, they will start to accumulate and affect the cleaning validation status of the equipment. Removal of air/liquid interface residues should be considered during the development of cleaning processes. These residues should also be removed manually when first detected, and until a validated effective cleaning process is implemented.

Maintenance Practices for Complex Systems – Highly automated systems require all components to work properly. System reliability becomes a challenge if individual components considered single points of failure start to fail (e.g., steam traps, gaskets use life). A risk assessment is recommended to evaluate which components should be emphasized in the maintenance reliability program and maintenance schedules (frequency of failure of components, useful life of gaskets in contact with product, etc.).

Drainability – Complex systems need to ensure full drainability of liquids after cleaning to ensure adequate Clean Hold Times (CHTs) and appropriate bioburden controls. Cleaned equipment intended for storage should be dried, usually accelerated by the use of Clean, Dry Air (CDA) (filtered air or nitrogen) after draining the system. Manual methods are commonly employed such as using a cloth or alcohol wipes, although these may be less reliable or not feasible for hard-to-reach surfaces.

Regulatory Harmonization and Mutual Recognition Agreements (MRA) – The developments in MRA between major regulatory agencies should drive toward greater harmonization of requirements and expectations. Cleaning validation can benefit from further alignment regarding the establishment of cleaning limits and overall management of a compliant cleaning program. During 2015, the PIC/S GMP Guide Annex 15 [9] was harmonized with EudraLex Annex 15 [4] to adopt HBEL as the basis for scientifically justified safe residue limits.

1.3.2 Key Terms

This section introduces key terms as they are used in the context of this Guide. Refer to Appendix 10 for an expanded listing of definitions.

Note: When calculating the cleaning threshold values, the terms PDE, ADE, and HBEL are used interchangeably in this Guide.

Acceptable Daily Exposure (ADE)

A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime [3].

Action Limit – also known as Action Level

A parameter set by the user that, when exceeded, requires immediate intervention, including investigation of cause, and corrective action [10].

Alert Level – also known as Alert Limit

A parameter set by the user that, when exceeded, gives an early warning of a drift from normal operational conditions, and should result in increased attention or corrective action [10].

Cleaning Agent

Chemical agent or solution used for cleaning. May be aqueous or solvent-based.

Detergent

A type of cleaning agent, usually aqueous-based and utilizing surfactants.

Health-Based Exposure Limits (HBEL)²

A daily dose or a substance below which no adverse effects are anticipated, by any route, even if exposure occurs for a lifetime. Derived from a structured scientific evaluation of relevant data [11].

Highly Hazardous Compounds

Compounds with low ADE/PDE values, for example, $\leq 10 \mu\text{g/day}$. (See the *ISPE Baseline® Guide: Risk-MaPP (Second Edition)* [3] Section 5.2 for further explanation.)

Limit of Quantitation (LOQ) – also known as Quantitation Limit (QL)

Lowest level of analyte that can be reliably measured with acceptable accuracy and precision.

Limit of Detection (LOD) – also known as Detection Limit (DL)

Lowest level of analyte that can be detected but not necessarily quantified.

Maximum Allowable Carryover (MACO) (also known as MAC)

Calculated quantity of residue from a previous product when carried over into a different product that can represent potential harm to the patient.

With the introduction of safe cleaning limits based on HBELs, the MACO term should be considered a Maximum Safe Carryover (MSC), which is the maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients [12]. For simplicity, this Guide has kept the terms MACO or Safe MACO to denote material carryovers from one product batch to the next product on shared equipment.

Nonhazardous Compounds

Compounds with high ADE/PDE values, for example, $\geq 100 \mu\text{g/day}$.

Permitted Daily Exposure (PDE)

A substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime [11].

Safety Limit (SL) – also known as Acceptable Residue Limit (ARL)

Represents the acceptable cleaning limit based on HBELs corresponding to a safe amount of residue in the next product dose (i.e., DP) or batch (i.e., DS)

² Establishing a HBEL involves the identification of hazard conditions (toxicity), evaluating the therapeutic or adverse effects, determining NOAEL (mg/kg/day), establishing a PDE or ADE, and calculating a MACO [11].

2 Cleaning Regulations

Regulatory agencies have provided guidance documents describing the expectations for cleaning to prevent contamination or adulteration of products. These guidance documents focus on requirements to ensure control of the cleaning process.

While regulations vary between countries, they are aligned in the general principles to confirm that pharmaceutical products are safe, efficacious, and free from adulteration by other components or contaminants. Table 2.1 contains frequently used guidance documents that describe expectations for compliant cleaning processes.

Table 2.1: Regulatory Guidances Related to Cleaning Validation

Regulatory Authority or Organization	Guidance
Canada	Cleaning Validation Guidelines GUIDE-0028 (2008) Canada Health Products and Food Branch Inspectorate Guidance Document [13]
China	GMP Annex 1: Sterile Medicinal Products, revised 2010 [14]
EMA (EU)	Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, November 2014 [11]
	EudraLex Volume 4 – Good Manufacturing Practice (GMP) guidelines, Chapter 5 – Production, March 2015 [15]
	EudraLex Volume 4, Good Manufacturing Practice (GMP) guidelines, Annex 15: Qualification and Validation, October 2015 [4]
	Questions and answers on implementation of risk-based prevention of cross-contamination in production and 'Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities,' April 2018 [7]
FDA (US)	21 CFR 211 (specifically 211.63, 211.65, 211.67, and 211.113) [16]
	Guide to Inspection of Validation of Cleaning Processes, 1993 [17]
	Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach, Final Report, 2004 [18]
	Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice, September 2004 [19]
	Guidance for Industry: Process Validation: General Principles and Practices, January 2011 [5]
	Guidance for Industry: Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, Questions and Answers, April 2018 [20]
ICH	Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients, November 2000 [21]
	Q9 Quality Risk Management, November 2009 [22]

Table 2.1: Regulatory Guidances Related to Cleaning Validation (continued)

Regulatory Authority or Organization	Guidance
PIC/S	Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PI 006-3 September 2007 [23]
	Guide to Good Manufacturing Practice for Medical Products, Annex 15, Qualification and Validation, 2015 [9]
	Aide Memoire: Cross Contamination in Shared Facilities, PI 043-1, July 2018 [24]
	Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities, PI 046-1, July 2018 [25]
	Aide Memoire: Inspection of Health Based Exposure Limit (HBEL) Assessments and Use in Quality Risk Management, PI 052-1, June 2020 [26]
	Questions and Answers on Implementation of Risk-Based Prevention of Cross-Contamination in Production and 'Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities', PI 053-1, June 2020 [27]
WHO	Technical Report Series, No. 957, Annex 2 WHO good manufacturing practices for active pharmaceutical ingredients, 2010 [28]
	Draft Working document QAS/20.849, Points to consider on the different approaches – including HBEL – to establish carryover limits in cleaning validation for identification of contamination risks when manufacturing in shared facilities, May 2020 [29]

In addition to these regulatory guidance documents, there are several industry guides, technical reports, and standards relevant to cleaning and cleaning validation such as those shown in Table 2.2.

Table 2.2: Cleaning and Cleaning Validation Industry References

3-A Sanitary Standards, Inc. (3-A SSI) [30]
APIC Guidance on Aspects of Cleaning Validation in Active Pharmaceutical Ingredient Plants (2016) [31]
ASME BPE - 2019 Bioprocessing Equipment [32]
ASTM E3106-18e1 Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation (2018) [33]
ASTM E3219-20 Standard Guide for Derivation of Health-Based Exposure Limits (HBELs) (2020) [12]
European Hygienic Engineering & Design Group (EHEDG) [34]
ISO 13408-4:2005 Aseptic processing of health care products – Part 4: Clean-in-place technologies [35]
<i>ISPE Baseline® Guide – Volume 7: Risk-Based Manufacture of Pharmaceutical Products [Risk-MaPP] (Second Edition)</i> (2017) [3]
PDA Technical Report No. 14, Validation of Column-Based Chromatography Processes for the Purification of Proteins (2008) [36]
PDA Technical Report No. 29, Points to Consider for Cleaning Validation (2012) [37]
PDA Technical Report No. 49, Points to Consider for Biotechnology Cleaning Validation (2010) [38]

3 Risk Management

3.1 Risk Management Description Overview and Regulatory Expectations

Quality Risk Management (QRM) is a rational approach to enable good decisions. Cleaning validation, like other GMP validation activities, is not exempted from the regulatory expectation of using risk management to control potential hazards, reduce risks, and establish sound cleaning processes. In fact, a risk-based cleaning validation strategy with justifiable and achievable acceptance criteria is crucial in attaining a compliant cleaning validation program.

For example, validation master plans for cleaning should either start with a documented risk assessment exercise or at least include the risk assessment process in the early stages of developing a new program. In today's pharmaceutical regulatory landscape, a retrospective risk assessment is not only a good practice, it is expected within cleaning programs, even if that program has been grandfathered as acceptable.

3.1.1 Regulatory Expectations

Quality risk management is a regulatory expectation, as noted in FDA's Pharmaceutical CGMPs for the 21st Century [18], which aims to encourage implementation of risk-based approaches that focus on critical areas for maintaining or improving product quality.

Expectations for the application of QRM principles to validation are clearly stated in regulatory documents.

For example, EudraLex Annex 15 [4] states applications for QRM in validation:

- To determine scope and extent of qualification and validation.
- To reassess risks after gaining more knowledge from commercial production.
- To determine criticality of process parameters.
- To evaluate planned changes to determine potential impact.
- To justify bracketing approaches.
- To determine the variable factors which influence cleaning effectiveness and performance.
- To justify selected cleaning limits.
- To justify the number of times the cleaning procedure should be executed (number of runs) for validation.
- To determine the risks presented by microbial and endotoxin contamination during the development of cleaning validation protocols.

Similarly, the FDA Guidance for Industry: Process Validation [5] calls for QRM principles to be applied:

- To determine the degree of controls needed to control process variation.
- To screen potential variables for Design of Experiment (DOE) studies to minimize the total number of experiments conducted while maximizing knowledge gained.
- To support the prioritization of certain equipment qualification activities and to identify the level of effort needed in both the performance and documentation of qualification activities.

- To justify the sampling location, sampling frequency, and confidence level for sampling plans.
- To determine criteria for process performance indicators.

Furthermore, EMA in its guidance for industry to set HBELs recognizes that cleaning is a risk reducing measure.

“A more scientific case by case approach is warranted for risk identification and to support risk reduction measures for all classes of pharmaceutical substances.” [11]

In addition, once a health-based assessment has been completed, the data is used as an input to a comprehensive risk management process to identify risks, determine controls necessary to address the risks, and evaluate if existing technical and organizational controls are adequate, or need to be supplemented with additional controls.

“It is expected that for products which present a higher potential harm to patients/animals, more elaborate organisational and technical control measures will be required. Using a structured Quality Risk Management process, manufacturers should consider the risks of cross contamination down to the established level from the HBEL. During the QRM study manufacturers should consider how easily such a quantity of contamination could occur, without detection, at batch and unit dose level.” [7]

The cleaning validation element of cross contamination control should be guided first by the HBEL and then consider the impact or contribution from other factors that influence the cleaning and requirements to ensure consistency and robustness in validation.

These expectations clearly demonstrate that risk management should be an integral part of cleaning validation efforts.

The premise that a company's quality system should include a formal risk management program further drives the need for cleaning validation to be approved by Quality Assurance (QA). It should have a foundation in observing, remediating, and controlling the risks inherent to any equipment that has been cleaned and ready for release for GMP use.

3.1.2 Risk Management Models

ICH Q9 [22] outlines a risk management process that is iterative and consists of the identification of hazards, and the analysis and evaluation of risks associated with exposure to those hazards, as well as control strategies to manage the risks. It has three distinct phases for the application of risk management: Risk Assessment, Risk Control, and Risk Review.

1. Risk assessment involves the identification of risks (hazards and their impact), the analysis of the risks, and the evaluation and prioritization of risks.
2. Risk control includes decision making to reduce/accept risks, create a control strategy, and communicate to stakeholders.
3. Risk review monitors the results of system performance and changes on a periodic basis, initiating additional risks assessments if needed.

During all phases, the output of each phase is communicated to stakeholders for appropriate knowledge management and decision making, especially after completing the Risk Control phase, where a control strategy is defined [22].

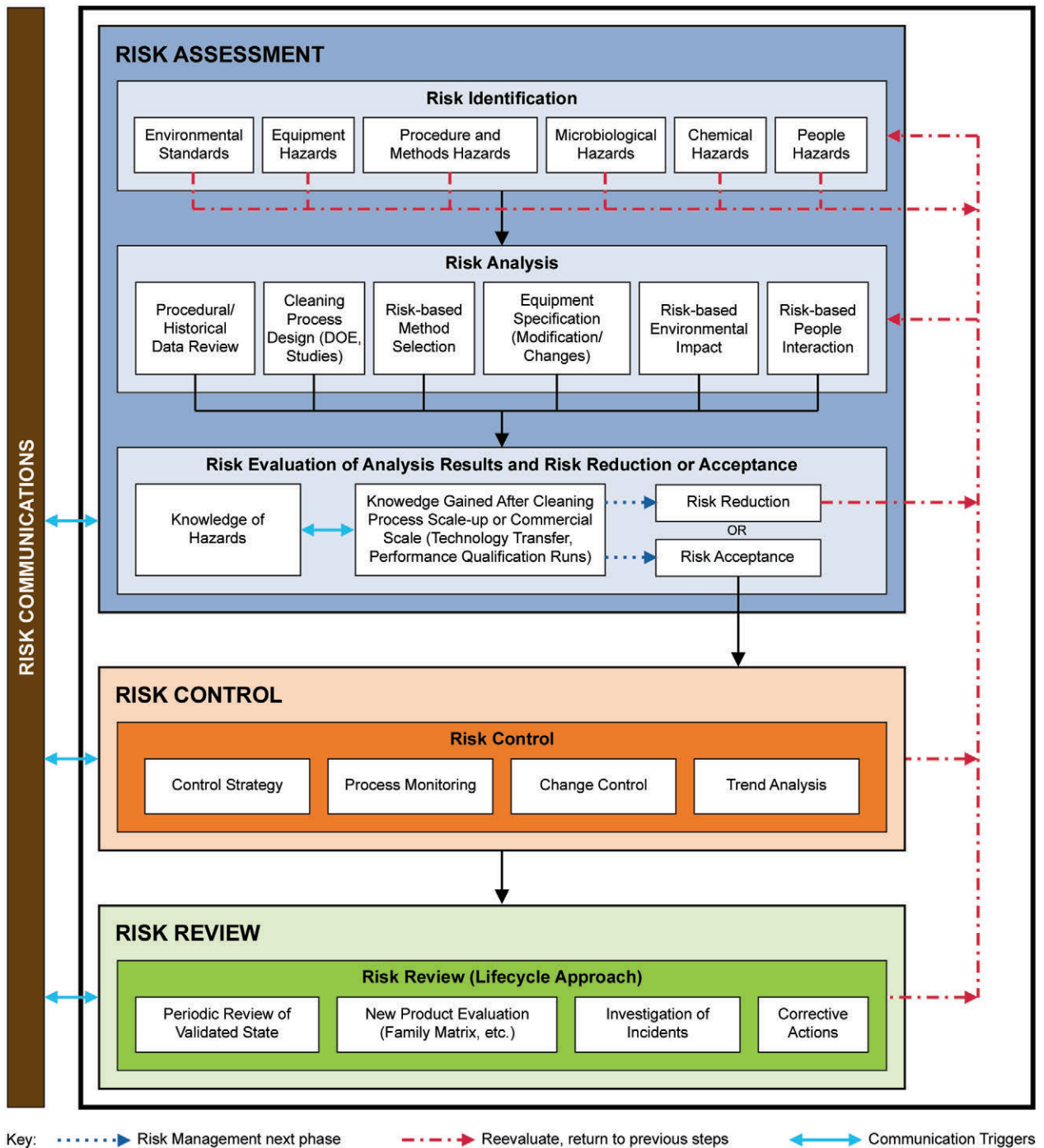
The risk management system should always be driven with a focus on the patient first, yet should not exclude potential impacts to the business, as the process must be considered sustainable with empirical data to support its claims.

Figure 3.1 adapts the ICH Q9 [22] model to cleaning risk management, linking cleaning validation activities with risk management principles.

- **Risk Identification:** Hazards from the environment, equipment, methods, chemical and microbial entities, and personnel are identified. The hazards may have an impact on the final residues after cleaning and therefore are considered risks.
- **Risk Analysis:** These risks are further analyzed to achieve a better understanding of the process and to prioritize their impact to cleaning. During this phase, process knowledge is increased by design reviews, data review, and studies to understand interactions between process parameters, equipment, environment, and personnel.
- **Risk Evaluation:** Risks are evaluated, and additional controls are identified to mitigate the risks (risk reduction) or accept the risk (risk acceptance).
- **Risk Control:** During risk control, final decisions are made regarding acceptable risks, and a control strategy is completed to ensure mitigating design, procedural, and technical controls are applied and remain in place. This control strategy is communicated formally to stakeholders.
- **Risk Review:** Risks are reviewed periodically or when significant or new hazards are introduced, such as the introduction of new products and after major incidents or events.

There is a relationship between QRM principles and the different phases of the validation lifecycle. As illustrated in Chapter 1, Figure 1.3, risk management is present throughout the validation lifecycle.

Figure 3.1: Cleaning Risk Management Process



There are many tools available to support the application of QRM principles. The most common are:

- Failure Mode Effects Analysis (FMEA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)

- Fishbone/Ishikawa

One hint to secure support between Subject Matter Experts (SMEs) and colleagues during risk assessments is to simplify (when possible) the logical path from supporting data to the outcome of the impact assessment. In-depth information on other risk assessment tools can be found in focused guidance from ISPE [3] or other reputable sources that give a full view of the tools for QRM use [39].

3.1.3 Sources of Variation

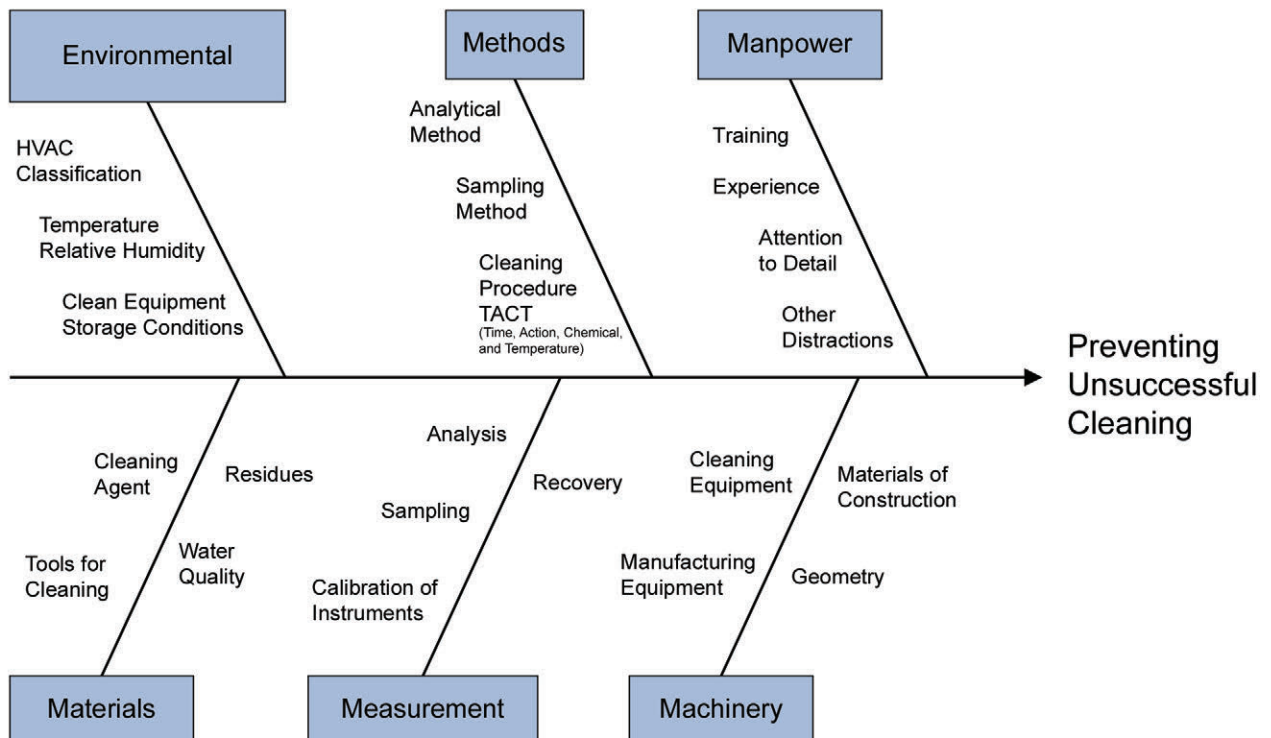
Unsuccessful cleaning of manufacturing equipment, including major and minor/ancillary equipment and change parts, as well as utensils, presents a risk to product quality and could ultimately impact patient safety if not adequately addressed.

One approach to take when determining causes of unsuccessful cleaning during or post cleaning validation is to start with an outline of the characteristics within the cleaning practices for risk assessment. The outline should identify the equipment, cleaning agents, Active Pharmaceutical Ingredients (APIs), types of products produced, microbial particulates/bioburden, lubricants, and procedures allocated to control the operational and cleaning processes. The cleaning procedures themselves can be a source of risk, especially manual procedures that have not been assessed in this manner; thus, a formal discussion on these materials and practices should be thoroughly documented.

The fishbone/Ishikawa diagram in Figure 3.2 provides an example³ of the sources of variation that could result in unsuccessful cleaning. From the fishbone outline, various impact assessment challenges can be derived using risk-based scenarios where failure could occur.

Figure 3.2: Potential Sources of Variation Related to Cleaning

Adapted from ISPE Training Slides [40]



³ The example provided herein is for illustrative purposes and is in no way meant to imply that this is the only way to perform the risk assessment process or risk identification task. Additionally, it is not intended to be an exhaustive, all-inclusive example.

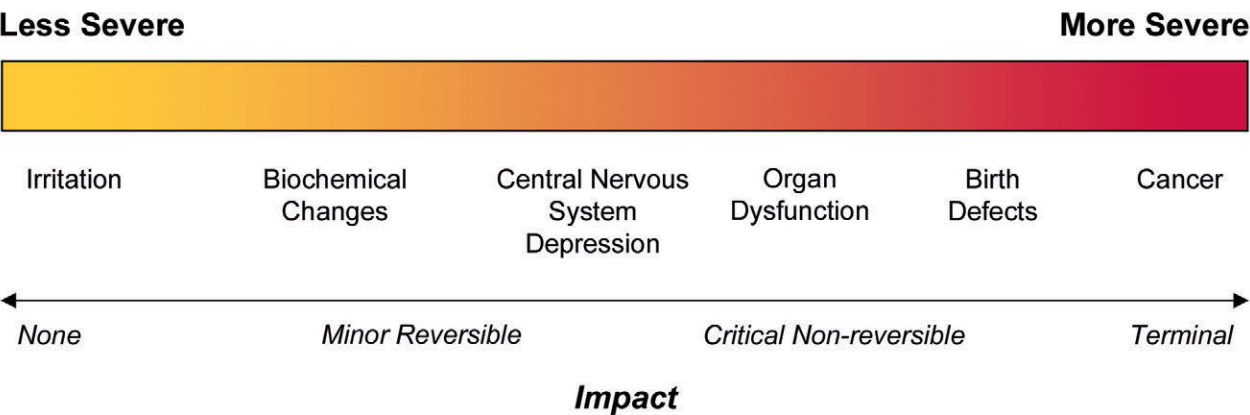
3.2 Risk Management Applied to the Cleaning Validation Program

Risk management for cleaning processes focuses on the hazard represented by the active and chemical residues on product contact surfaces, the impact or severity represented by such residues, the likelihood of these residues being present, and the ability to detect them.

Many cleaning regimens originally focused on visual cleanliness as a measure of success. However, there are multiple sources of hazards in a cleaning process that need to be well understood in order to guide the planning and decision making for developing effective and compliant cleaning processes.

One of the most important hazards in a cleaning program comes from the type of soils to be cleaned. Some chemicals and actives present low risks to patients and others higher risks, as represented in Figure 3.3.

Figure 3.3: Hazard Continuum [3]



The recommended approach for protecting patients from chemical and active residue is to use toxicological data to determine the residue HBELs, and then use the results to set cleaning limits. This approach is strongly encouraged by the EMA: Questions and answers on implementation of risk-based prevention of cross-contamination in production and ‘Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities’ [7], Question 3:

“Once the health-based assessment has been completed and the HBEL confirmed, these data should be used via a Quality Risk Management process to determine what controls need to be put in place and to assess if existing organisational and technical control measures are adequate or if they need to be supplemented. This Quality Risk Management process should be carried out prospectively in the case of new equipment/facility to determine what control measures are required.”

Additionally, organizations need to implement appropriate technical and procedural controls commensurate to the risks for contamination. The QRM process should consider cross contamination risks down to the established HBEL and evaluate how the risks may impact a batch or unit dose [7].

Table 3.1 lists a summary of specific applications of QRM to cleaning validation.

Table 3.1: Examples of QRM Applications in Cleaning Validation

Cleaning Validation Milestone	Tasks	Considerations
Validation Master Plan	Matrix approach or testing all products (multiproduct facility)	Define “worst-case” approach for validating products and API
	Define sampling plan	Sampling methods, locations, frequency, and confidence levels
	Selection of analytical methods	HPLC versus Total Organic Carbon (TOC) along with appropriate microbial testing techniques, LOD, method variability
Design and Development	Determine target HBEL and perform risk assessment to evaluate cleaning limits	Availability of PDE/ADE or clinical data Impact to existing control plans
	Determine parameters for the cleaning process Justify bracketing and grouping approaches	Determine interactions between parameters and justify best ranges for effectiveness and performance
Qualification (PPQ)	Test equipment hard to clean areas to confirm CV	Confirm equipment is sufficiently clean to complete CV through appropriate testing and sampling locations
	Determine number of runs for cleaning qualification	Optimum number of times cleaning procedures must be executed to cover the scope of cleaning validation
Verification (CPV)	Find areas where the processes can be improved	CHT studies or reduced testing strategies during campaigning production, evaluation of current hazards to update controls
Ongoing Monitoring	Ensure that cleaning limits remain appropriate and that periodic testing satisfies requirements	Additional process knowledge could change initial PDE/ADE calculations; verification via spot checking the current hazards can reduce risk
	Evaluate opportunities for reduced testing	Level of controls (testing) should be commensurate to current level of risks
Periodic Review	Assemble a cross-functional team for assessment to evaluate and report on the cleaning validation program effectiveness	This report should be available for regulatory review to highlight updates in cleaning validation control strategies
Change Management	Evaluate planned changes to determine potential impact	Consider impact to validation control plan. Consider accumulative impact of changes.

Additional risk evaluation applications are discussed in Sections 3.2.1 to 3.2.4 using the cleaning validation lifecycle.

3.2.1 Initial Cleaning Validation Assessments

Validation assessments at this stage help determine the scope and extent of qualification and validation efforts from a perspective of risk.

The assessment conclusion should recommend validation, verification (i.e., dedicated indirect equipment), or no validation (i.e., waste collection vessels) requirements. The assessment should also identify the extent of the effort (number of runs or products involved, studies anticipated to be needed, special training considerations, etc.). Table 3.2 provides a list of areas to consider during assessments for validation.

Table 3.2: Validation Assessment Elements for Cleaning

Scope	Evaluation Scope
Analytical Methods	- Supplies (e.g., containers, swabs) - Specificity - Robustness - Range - Sensitivity - Active degradation - Procedure for unknown peaks
Cleaning Agents	- ADE/PDE levels - Cleaning effectiveness - Rinsability - Detectability
Cleaning Cycle Development	Number of runs
Cleaning Procedure	- TACT* characteristics - Reproducibility (e.g., automated, semiautomated, manual) - Level of training - Level of detail (e.g., manual cleaning)
Cleaning Qualification Execution	Number of runs
Hold Times	- Dirty (e.g., effect on cleanability) - Clean (e.g., length, storage, proliferation)
Manufacturing Equipment	- Equipment and process product contact points - Equipment complexity (e.g., components, circuits, shape) - Buildup concerns - Grouping (e.g., products, equipment)
Manufacturing Process	- Soil cleanability - Process step criticality - Soil load/batch size variation
Residue	- ADE/PDE levels of process residues (e.g., APIs, excipients, degradants, process aides, lubricants) - Cleanability - Detectability
Safety Cleaning Limits	- Cleaning limit calculation and justification - Rationale for chosen cleaning limit method - HBEL safety limit calculation and justification
Sampling Approach	- Indirect (e.g., timing, sequence (in-line, grab sample, separate)) - Direct (e.g., accessibility, locations) - Visual inspection (e.g., accessibility, lighting)
Sampling Recovery	- Recoverability (cleaning agent, active ingredient, and microbial) - Materials of construction - Percent recovery
*TACT = Time, Action, Chemical, and Temperature	

3.2.2 Introduction of New Products Risk Assessments

Introducing new products into a facility requires in-depth knowledge of the new hazards this may imply. When assessing the validation effort for legacy cleaning processes, the assessment should consider factors such as:

- Historical knowledge of current processes

- Process and equipment similarities
- Cleaning methods used
- Cleaning agents used
- Equivalent or worst-case excipients/formulations

If the new product to be introduced does not represent a new worst-case chemical or active to clean, then the existing cleaning process may be considered sufficient. A comprehensive risk assessment is completed to evaluate any changes to the existing control plans, including updating justification reports for HBEL, sampling, and all other elements of the cleaning program. Conversely, if the new product introduces new chemicals or actives that exceed the capability of the current cleaning process, then a comprehensive evaluation of the cleaning program is required.

Refer to Appendix 8 for a case study applying QRM principles to the introduction of new products in an existing facility.

3.2.3 Ongoing Monitoring Maintenance Risk Assessments

The level, type, and frequency of testing during the ongoing monitoring of a validated cleaning process is evaluated via an initial risk assessment. This ensures the implementation of a monitoring program that is science and risk-based. Additionally, as risk is reduced, the level of monitoring can be reduced.

The scope of the risk assessment should be determined early in the process, ideally as part of the Validation Master Plan (VMP) and periodic review of cleaning processes.

3.2.4 Routine Operation of Cleaning Process Risk Assessments

As part of the ongoing verification of cleaning processes, a risk assessment is performed to assess the cleaning process for changes in hazards and corresponding risks. It assesses changes in processes, procedures, activities, and determines points of highest impact. The assessment should be a living document to be updated on a periodic schedule (i.e., during cleaning periodic reviews) or be part of a control strategy to capture changes to the process.

HACCP or modified versions are good for assessing the process and determining potential failure points or weak points within the process.

Considerations:

- Changes documented as part of the cleaning process periodic review
- In-process sampling methods
- Process performance
- Changes in manufacturing process steps
- Changeover procedures
- Training program
- Changes in CIP/COP recipes and alarms
- New product and equipment grouping
- Equipment maintenance

3.2.5 Additional Applications

For complex processes or scenarios, separate risk assessments can be used to evaluate special hazards and identify appropriate control measures to mitigate risks. For example:

- Implementing an aggressive cleaning validation grouping strategy
- Using reduced Material of Construction (MOC) recovery groupings to represent larger groups of materials
- Optimizing the level of detail for non-critical manual cleaning activities

These scenarios require that SMEs understand how to effectively analyze and control potential hazards. The output of these risk assessments is used to support better decisions.

3.3 Points to Consider When Using QRM Tools for Cleaning Programs

The risk evaluation approaches in this section can be tailored for the initial cleaning validation process, a new product introduction (i.e., legacy process), or maintenance of the cleaning program (i.e., CPV and periodic review). They are presented as an example for illustrative purposes and are not meant to be an exhaustive list. Each company applies the appropriate considerations for risk evaluations aligned with their risk procedures and hazards. Comprehensive applications of these concepts are found in the *ISPE Baseline® Guide – Volume 7: Risk-Based Manufacture of Pharmaceutical Products [Risk-MaPP] (Second Edition)* [3].

3.3.1 Severity

When evaluating severity, a decision must be made to assess toxicological severity (i.e., low ADE/PDE values (high hazard), biological, topical) from an industry or site perspective. It is recommended to assess risk from a patient perspective. Table 3.3 presents a list of considerations when assessing severity.

Table 3.3: Assessing Severity – Topics to Consider

Severity	Examples of Rating Factors				
	5	4	3	2	1
Equipment Use	Shared				Dedicated
Direct or Indirect	Product		Excipient		Buffers
Type of Product	Low ADE/PDE (high hazard)	Rx (Prescription)	Over the Counter (OTC)	Nutritional	Cosmetics
HBEL	≤ 1 µg/day		≤ 10 µg/day		≥ 100 µg/day
Stability of Active	Stable	25% deactivated/ degraded	50% deactivated/ degraded	75% deactivated/ degraded	Completely deactivated/ degraded
Route of Administration	Intravenous		Oral		Topical
Cleaning Agents	Formulated		Commodity		Water only
Microbial Concerns	Dry manufacturing processing step	Dry processing	Bacteriostatic or low-water activity Process material	Sanitization steps prior to use	Sterilization steps prior to use
Proximity to Patient or Further Purification Steps	Filling*	Formulation*	Final Purification	Initial Purification or Recovery	Fermentation

*For drug product facilities, the risk factors could be 5 and 1 for filling or tableting, respectively. 5 = High Severity / 1 = Low Severity

3.3.2 Probability

“What is the likelihood (probability) it will go wrong?” [3]

Table 3.4 provides a list of considerations when assessing probability.

Table 3.4 Assessing Probability – Topics to Consider

Probability	Examples of Rating Factors				
	5	4	3	2	1
Soil Type	Pastes		Solids		Liquids
Cleanability (Due to Solubility or Manufacturing Process)	Difficult to clean		Moderately hard to clean		Easy to clean
Cleaning Reproducibility	Manual		Semiautomated		Automated
Equipment Design	Complex geometry and high number of internal components	Simple geometry and high number of internal components	Complex geometry with low number of internal components	Simple geometry with low number of internal components	Simple geometry with no internal components, except valve
Microbial Load	Ambient process water (WFI or PW) cleaning solutions	Bacteriostatic or low-water activity Process material	Hot process water (WFI or PW) cleaning solutions	Caustic and/or acidic cleaning solutions	Steam in Place (SIP) or sanitization steps prior to use
Deviations	Cleaning failures due to cleaning process failure		Cleaning failures due to system failures		No known cleaning failures
Age of Cleaning Validation	Over 20 years	16 to 20 years	11 to 15 years	6 to 10 years	Under 5 years
CV Results (Worst Case)	Above 51%	21%–50%	10%–20% of limit	Below LOQ	Below LOD
Historical Routine Monitoring Trending Data	Historically outside of sigma		Variable trending history		Consistent trending within sigma
5 = Higher Likelihood / 1 = Lower Likelihood					

3.3.3 Risk Prioritization⁴

There are many approaches to prioritizing risks. It is critical to establish definitions and ranges for risk potentials. Risk Priority Numbers (RPN) can be derived from a matrix or algorithm that takes into consideration the likeliness, detection, and impact of risks to produce a scalable value. Once the risks are prioritized, a mitigation strategy can be agreed to. Table 3.5 presents an FMEA scoring table as an example to help determine relative priorities of risks.

Table 3.5: Sample FMEA Scoring [3]

RPN Value	Severity	Occurrence	Detection
10	Injury to a patient or employee; ADE < 1 µg/day	More than once per batch	Not detectable by current methods
7	Cause extreme customer dissatisfaction; ADE = 1 > 10 µg/day	Once per batch	All manually inspected
5	Something likely to result in a complaint; ADE = 10 > 100 µg/day	Once per six months	Statistical sampling
3	Minor nuisance resulting in no loss; ADE = 100 > 1000 µg/day	Once every one to three years	100% inspection
1	Be unnoticed and not affect performance; ADE ≥ 1000 µg/day	One occurrence in greater than five years	Obvious or controlled and monitored and alarmed by control system

⁴ A core element of the FMEA tool is to use risk scores. Scoring is arbitrary and as such extreme caution should be applied when scoring is used as a decision-making process for risk mitigation. Approaches to set risk scores (e.g., RPN) should be defined by qualified personnel and supported by a sound, consistent, and thoroughly documented process.

4 Cleaning Validation Principles

4.1 Cleaning Validation Lifecycle

Cleaning is considered a critical process in the manufacturing of pharmaceutical products [41]. A traditional cleaning validation program places emphasis on demonstrating that the cleaning method works as intended through a qualification program. However, current practices recognize that a better approach is to treat cleaning validation as a lifecycle, where the emphasis is shifted from performing cleaning qualifications to performing cleaning development and ongoing cleaning verification during the use of the cleaning method.

The cleaning validation lifecycle follows the model defined by FDA [5], the concepts defined in the EMA Process Validation Guideline [6], and other regulatory bodies for process validation.

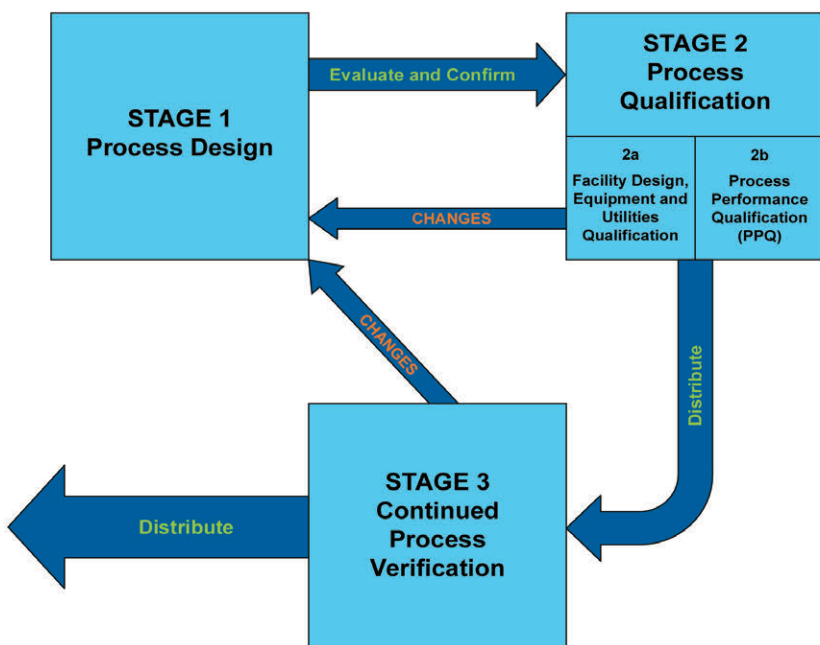
“Although the rigor of process design and the timing of implementation for some ‘stages’ may differ, the science and risk-based methodology described in the FDA guidance is equally applicable to cleaning processes.” [3]

For existing operations and processes, the introduction of new products or residues may require an assessment of the suitability of existing cleaning method designs, rather than forcing a new design of cleaning methods.

The main elements of the FDA lifecycle model [5] are illustrated in Figure 4.1. The lifecycle model adopts the principles of Quality by Design, which states that quality cannot be assessed by testing alone. Therefore, processes need to be developed, critical parameters need to be identified, and the cleaning process monitored to verify ongoing performance and ensure quality output. The quality output expected from a cleaning process is the achievement of consistent cleaning of manufacturing product contact surfaces at a target cleanliness level that represents no harm to patients or impact to product quality (safety, identity, strength, potency).

The lifecycle approach for cleaning validation is more comprehensive than the traditional approach as application of the lifecycle ensures that the cleaning process remains in a state of control and provides a logical progression for gaining knowledge for process improvements. A comparison between the approaches is summarized in Table 4.1.

Implementing a lifecycle approach can be challenging for legacy products where the development of the cleaning process may not be fully documented. However, a company can benefit from understanding the cleaning process parameters and design constraints when dealing with cleaning method changes or investigating failures. Better knowledge of the cleaning process provides the tools necessary to assess potential manufacturing cross-contamination risks and helps to ensure a compliant and effective cleaning program.

Figure 4.1: FDA Model of Process Validation Lifecycle*Adapted from the FDA Presentation “Process Validation, A Lifecycle Approach” [42]***Table 4.1: Comparison Between a Traditional Approach and a Lifecycle Approach to Cleaning Validation**

Traditional Approach	Lifecycle Approach
- Identify APIs and chemicals to clean - Select and qualify cleaning agents - Create Standard Operating Procedures (SOPs) for cleaning equipment - Determine cleaning procedure parameters - Establish sampling plan (sampling locations and methods) - Select validated analytical methods - Complete recovery studies - Develop acceptance criteria - Select equipment groups or families to simplify validation - Determine number of runs for validation (minimum of 3 runs considered acceptable) - Write validation protocol - Qualify equipment and methods - Train personnel - Execute cleaning validation protocol - Maintain ongoing control via change management - Monitor cleaning periodically	- Stage 1 – Cleaning Process Design: Typical activities include creating a cleaning validation plan, selecting cleaning agents, determining Health-Based Exposure Limits (HBEL), defining critical parameters following Quality Risk Management principles, characterizing residues, evaluating parameter interactions, completing recovery studies, selecting validated analytical methods, reviewing equipment design, grouping equipment, defining limits and acceptance criteria. - Stage 2 – Cleaning Process Qualification: Typical activities include conducting next phases of the validation plan, qualifying equipment, reviewing utilities readiness, qualifying suppliers, selecting sampling site, justifying number of qualification runs, creating a cleaning qualification protocol, training personnel, executing the cleaning qualification protocol, and issuing the final validation report. Knowledge gained during this stage may require going back to Stage 1 for further development. Otherwise, proceed to Stage 3. - Stage 3 – Continued Cleaning Verification (Ongoing Cleaning Verification): Typical activities include establishing periodic reviews, determining extension of PV sampling and testing, monitoring process capabilities, reviewing deviations and changes. Knowledge gained during this stage may require going back to Stage 1 for further development or for revalidation at Stage 2.

It is possible to introduce changes to previous stages in the lifecycle model based on knowledge gained during the execution of each stage. Risk-based approaches and assessments are conducted throughout the lifecycle, especially during Stage 1 and Stage 2 of the model.

Application of the Process Lifecycle Model to Cleaning Validation

The process lifecycle approach is a way to standardize a company's manufacturing and cleaning process [41]. There are three stages defined in the FDA process validation approach [5]: Stage 1: Process Design, Stage 2: Process Qualification, and Stage 3: Continued Process Verification. Similar terminology can be found in other regulatory guidances (see Table 4.2). The following analogous terms are defined for the cleaning process lifecycle:

- Stage 1: Cleaning Process Design – The cleaning process is defined based on knowledge gained through development and scale-up activities.
- Stage 2: Cleaning Process Performance Qualification (Cleaning PPQ) – The cleaning process is executed to demonstrate that the process, as developed and designed, produces the expected results in a reproducible manner.
- Stage 3: Continued Cleaning Process Verification – Ensures that critical cleaning process variables are monitored and that the process operates in a state of control.

A Cleaning Validation Master Plan (CVMP) can be created as early as in Stage 1 to cover design aspects of cleaning validation. The CVMP outlines the principles involved in the qualification of cleaning equipment, utilities, systems, and validation of cleaning processes. The CVMP also describes the written program to achieve and maintain a validated cleaning process. The information for a CVMP can also reside in an overarching facility VMP. Refer to Section 4.3 for additional details.

Table 4.2 compares the process validation regulatory stages with the terminology used in this Guide.

Table 4.2: Goals and Typical Activities of the Stages of Process Validation and Cleaning Validation

Adapted from Table 2.1 in ISPE Good Practice Guide: Practical Application of the Lifecycle Approach to Process Validation [43]

Stage of Validation	Process Validation Terminology	Goals	Cleaning Validation Lifecycle Approach Terminology Used in this Guide
Stage 1	Process Design (FDA/WHO) [5, 44] Pharmaceutical Development (EU) [45]	Define and design process	Cleaning Process Design
Stage 2	Process Qualification (FDA/WHO) [5, 44] Process Validation (EU/PIC/S) [4, 9]	Process is executed to demonstrate the process is capable of reproducible commercial manufacturing Cleaning process is executed to demonstrate that the process produces the expected results in a reproducible manner	Cleaning Process Performance Qualification (Cleaning PPQ)
Stage 3	Continued Process Verification (FDA/WHO) [5, 44] Ongoing Process Verification (EU/PIC/S) [4, 9]	Ongoing assurance that the process remains in a state of control	Continued Cleaning Process Verification



Table 4.3 provides a cross-reference between cleaning lifecycle phases and this ISPE Guide chapters relevant to the topic.

Table 4.3: Cleaning Validation Lifecycle Topics and Chapter Cross-References

Lifecycle Phase	Topic	Chapter References
Design	1. Define requirements and risk-based approaches	2, 3, 4.1.1, 5.6, 6.1, 6.2, 6.3, 6.4, 6.5, 7.4.1, 10.4, 11.1
	2. Complete residue characterization	4.1, 4.1.1, 5.1, 5.6
	3. Select cleaning agents	4.1.1, 5.2.7, 5.5, 5.6.2, 5.7
	4. Select cleaning process parameters	4.1.1, 5.5, 6.5.3, 10, 17, 18
	5. Select cleaning methods	4.1.1, 5.1, 5.4, 5.6.2, 5.7
	6. Review equipment design	5.2, 5.3, 10
	7. Determine residue limits	6
	8. Select analytical methods	5.6.2, 8
	9. Select microbial methods	8.2
	10. Define sampling methods and complete recovery studies	6.5, 7
	11. Determine acceptance criteria	6
	12. Complete small-scale studies	5.6.2, 5.8.1.1
Qualification	13. Determine readiness of equipment, methods, utilities	4.1.2, 4.4, 8
	14. Define validation strategy, number of runs	3.2, 4.1, 4.2, 4.3, 4.4, 5, 5.6, 6.4
	15. Define sampling plan	4.1.2, 4.4, 7
	16. Define visual inspection criterion	6.3
	17. Complete SOPs	4.2, 4.4
	18. Complete cleaning validation protocol	4.4
	19. Complete personnel training	4.1.2, 5.4, 6.3
	20. Execute validation runs	4.4
	21. Complete validation report	4.4
Continued Verification	22. Execute cleaning monitoring	4.1.3, 6.3.1, 6.4
	23. Execute periodic reviews	4.5
	24. Execute product changeover procedures	4.1.3
	25. Evaluate change control	4.6, 11

4.1.1 *Cleaning Process Design*

During the process design stage, the cleaning process variables are set, the criticality of parameters are assessed, and CIP/SIP cycle development (as applicable) and scale-up activities are completed. Small-scale, pilot, or laboratory studies are conducted to support the development effort in defining the cleaning process. The cleaning process design effort can be documented in a validation strategy document or plan. This overall strategy entails understanding the regulatory and operational requirements for cleaning, and any other equipment-related considerations (refer to Chapter 5).

Important Stage 1 elements are:

- **Residue Characterization:** An evaluation is performed to determine the characteristics of the soils to be cleaned (product, excipients, location, cleaning agents, dyes, foreign material, etc.). Aspects such as solubility, concentration, cleanability, and conditions for degradation or deactivation of residues are considered in the assessment.
- **Select Cleaning Agents:** Selecting cleaning agents is one of the first steps in developing a cleaning process. There are many options (e.g., water, solvents, chemicals, formulated cleaners). Knowing what needs to be cleaned (product, residues, cell growth media, proteins, dyes, etc.) and the type of surface to be cleaned will help in selecting the appropriate cleaning agent for the application. The cleaning agent should be compatible with the MOC of the surface to be cleaned, and have the appropriate capacity to dissolve, loosen, or impact the product/soil characteristics to be removed. Some cleaning agents are considered a type of residue in the cleaning program, and need to be removed below the established cleaning and SL. The selection of cleaning agents should be justified by laboratory studies that take into consideration the type and condition of the soil to be cleaned, the cleaning agent parameters (e.g., time, action, concentration, temperature) and the cleaning method to be used. Another consideration for selecting a cleaning agent is the level of degradation of APIs by the detergent. The extent of degradation may impact toxicity assessments and the analytical methods needed to support the cleaning process.

The environmental impact of the disposal of cleaning agents into process streams or treatment facilities is an important consideration. Cleaning agent suppliers play an important role in ensuring consistent material quality. Suppliers may use different components in their manufacturing process that may impact the type of residues a company needs to clean.

- **Select Cleaning Process Variables and Justification of Criticality:** The identification of cleaning process parameters and justification of which ones are critical for process effectiveness are important elements to define during this stage. Typical parameters include:
 - Concentration of cleaning agents
 - Sequence of cleaning agents if more than one is used
 - Volume
 - Temperature
 - Time
 - Cleaning agent force (velocity for physically removing residues)
 - Number of cleaning cycles required
 - Need for initial rinse cycles

- Recirculation rinses
- Duration of blowdowns or drying cycle

Process parameters that can directly impact the effectiveness of a cleaning method should be considered critical. The objective is to define the cleaning process by defining the normal operating range for critical parameters, understanding the interactions between parameters, and determining any point of failure for the intended operating ranges. DOE methodologies can be used to determine the optimum ranges of cleaning process parameters in automated systems to prevent over-extending the time required to clean equipment. DOE can also accelerate the development of CIP cycle parameters. A short and effective cleaning process will maximize production capacity and overall productivity. A safety factor or contingency should be added to optimal productivity cycles to ensure the safety HBEL values are always met.

- **Select Cleaning Methods:** During Stage 1, the cleaning methods are selected, such as:

- Manual cleaning
- Clean out of Place (COP)
- CIP
- Soaking
- Ultrasonic treatments
- Pressurized wash
- Flooding
- Pre-cleaning treatments
- Immersion in cleaning agents

Refer to Chapter 5 for more details on cleaning methods.

- **Review Equipment Design and Inspection Procedures:** The knowledge developed in laboratory and pilot plants needs to be assessed against the equipment design and inspection procedures to ensure that the recommendations are properly applied and implemented. Equipment design and inspection procedure considerations include:
 - Coverage tests (e.g., riboflavin tests)
 - Results of laboratory test coupons
 - Condition of equipment surfaces (e.g., free of scratches, free of rouge)
 - Piping drainability
 - Dents
 - Surface finish
 - Level of light to conduct visual inspections

- Internal vessel configurations
- MOC

Dead legs need to be identified and opportunities for hold up of residues that require equipment to be dismantled for cleaning (as is common in solid dose manufacture) need to be identified and then either designed out if possible or dismantling built into cleaning processes. Flow rates through piping should be sufficient to prevent accumulation of residues and ensure full coverage of solutions. The MOC should be based on the process and the ability to clean. Stainless Steel (SS) vessels are common in the pharmaceutical industry, and are susceptible to corrosion under certain conditions. If groupings or bracketing of equipment are planned to simplify the validation effort, an equipment grouping comparison should be completed as part of the design review. Equipment groupings or bracketing can be justified for the same type of equipment (e.g., size, configuration, MOC, complexity) and the same cleaning procedure.

- **Determine Residual Limits and Overall Acceptance Criteria:** Acceptance criteria for residual limits should be set before assessing other parameters. Refer to Chapter 6 for a detailed explanation on the determination of limits and acceptance criteria. The overall cleaning acceptance criteria should include not exceeding the HBEL, cleaning limit (including action levels to ensure cleaning process control), and microbial control parameters, as well as achieving a successful visual inspection of selected cleaned surfaces. Refer to Section 6.3 for a detailed explanation of visual inspection.
- **Select Analytical Methods:** Selection of analytical methods is made taking into consideration method selectivity (for product specific methods), LOD or LOQ, and the method validation status. All methods should be validated before use. Specific methods are preferred; however, if it is not feasible to test for specific product residues, other representative parameters may be selected, for example, TOC. Refer to Chapter 8 for more details on analytical methods.
- **Select Microbial Methods:** The selection of appropriate microbial methods and the determination of initial alert level and action limits, sampling methods justification and selection, and necessary recovery studies are defined in this stage. Refer to Chapter 8 for additional details on microbial methods.
- **Define Sampling Methods and Recovery Studies:** Sampling methods are selected during the cleaning process development. Refer to Chapter 7 for additional information regarding sampling methods, and Sections 6.5, 7.1, and 7.2 for information on recovery studies.

4.1.2 **Cleaning Process Performance Qualification**

Stage 2 of cleaning validation can be divided in two subsections. Stage 2.1 is concerned with equipment readiness, including utilities. Stage 2.2 addresses the qualification and performance of the cleaning process.

The important aspects of Stage 2 are:

- **Determine Readiness of Equipment, Analytical Methods, and Utilities:** Before validating processes, the technical systems, equipment, utilities, and other supporting systems need to be qualified. Equipment qualification precedes validation activities and consists of challenges and tests to verify that the equipment was constructed per design, installed properly, and operates as intended within its required functionality. Qualification protocols are executed to document equipment readiness. Important for cleaning processes is the verification of proper operation of spray devices and their coverage. Visualization agents (e.g., riboflavin tests) are effective in verifying spray nozzle coverage. The qualification of automation and computerized systems is also verified (programmable logic controllers, CIP automated systems, etc.). These qualification activities need to be completed prior to starting cleaning process performance qualification runs.

Utilities and corresponding distribution systems critical to the cleaning process need to be qualified. These include water (such as those defined in the USP [46]), clean steam, and gases (e.g., nitrogen, air).

Analytical methods readiness includes identification of those analytical methods that need to be validated and the methods to be transferred to the appropriate testing laboratory. Sampling methods via rinse or swabs should also be validated. Refer to Chapter 8 for more details.

- **Define Validation Strategy, including Cleaning Validation Protocol and Number of Runs:** Approved protocols are required to execute a cleaning PPQ. They consist of executing the cleaning process on soiled equipment to demonstrate the effectiveness and reproducibility of the cleaning process. The protocol should define and justify the number of cleaning validation runs, CHT (the amount of time cleaned equipment can remain in a cleaned state), Dirty Hold Time (DHT: the amount of time soiled equipment can remain dirty before cleaning), and drying time as part of the cleaning process. Refer to Chapter 5 for additional details.

A cleaning PPQ needs multiple successful execution runs of the cleaning process to demonstrate process consistency. The number of PPQ runs to validate a cleaning method should be risk based and requires a documented rationale established on an understanding of the cleaning process, data obtained from the design and development of the cleaning process, and data from similar cleaning methods.

- **Define Sampling Plan:** A sampling plan describing sampling locations, number of samples, and the types of samples is prepared and integrated into the cleaning PPQ protocol for execution. Refer to Chapter 7 for more information on sampling.
- **Complete SOPs and Determine System Parameters:** SOPs describe the steps and specific instructions required to execute a cleaning process, and should be approved prior to starting PPQ runs. Automated systems have system configurations with appropriate parameters defining the sequence of steps to be executed for cleaning. These parameters define recipes for cleaning and should be clearly documented.
- **Complete Personnel Training and Qualification:** Personnel (i.e., operators, laboratory technicians, samplers, and inspectors) have the necessary education and experience, and are trained on SOPs related to the cleaning process and on the cleaning validation protocol content and objectives. If necessary, the training program includes operational details to ensure equipment is dismantled and assembled correctly. Personnel also receive on-the-job training to be able to execute procedures, document observations properly (e.g., visual inspections), and detect unexpected events. Effectiveness of on-the-job training is important to document the ability to execute the cleaning procedure as written. Training always precedes qualification.
- **Execute Cleaning PPQ:** Approved cleaning protocols are executed, and data (e.g., parameters, observations, CIP cycle start/stops) is documented for assessment against critical cleaning method process, critical parameters, and acceptance criteria. Refer to Section 4.4 for additional details. Cleaning validation is not required for clinical batches; instead, cleaning verification testing is performed based on the knowledge and criteria developed during Stage 1.
- **Complete Final Cleaning Validation Report:** The final validation report consists of several sections including:
 - Report approval
 - Executed protocols
 - List of products and equipment included in the cleaning validation study
 - Validated parameters and ranges
 - References to the cleaning procedures used
 - Discussion of failures and investigations that occurred during validation (visual and analytical results)
 - Plans for CPV and periodic reviews

- Conclusions

An important consideration should be an assessment of the final level of risk from the hazards and controls as demonstrated during the qualification runs. Future changes to equipment or product introductions will require ongoing analytical assessment, especially for low HBEL products. A justification should be documented in the validation report if the assessment of the final level of risks is deemed unnecessary. Prior to issuing a final report, interim reports may be issued. The interim report is similar to a final report (including QA approval) except that it only relates to some of the qualification runs from the cleaning plan.

4.1.3 **Cleaning Process Continued Verification**

During this stage, the cleaning process is monitored to ensure it is operating in a state of control. The main aspects of Stage 3 are:

- **Ongoing Cleaning Monitoring:** Through process monitoring, unplanned events representing a departure from the validated process can be detected. Data from process monitoring should be trended to detect shifts in cleaning method performance. The monitoring program should be risk based and mindful of the hazards and level of confidence established through the cleaning validation. The monitoring program can be a subset of tests utilized during the cleaning PPQ, and should include a sampling plan and should list all of the analytical methods to use. Refer to Section 6.4 for additional information regarding process control.
- **Periodic Review:** A comprehensive evaluation of the cleaning process state is performed as part of the validation lifecycle. The intention of the review is to demonstrate that the cleaning process remains in a validated state of control. The outcome of a periodic review may include recommendations for process improvement or for revalidation if the cleaning process is found out of control. Refer to Section 4.5 for more details.
- **Product Changeover Procedures (PCO):** PCO procedures should be in place. Risk-based methodology, along with historical performance, should be used to determine when to initiate PCOs.
- **Additional Controls:** Validated cleaning processes are subject to change control. Refer to Chapter 11 for more details. A preventive maintenance program is in place to maintain the equipment in an operational state. In addition, unexpected events representing failures to the cleaning process are documented as deviations. For example, an unsuccessful manual cleaning that does not meet the acceptance criteria must be documented prior to recleaning following an approved procedure. This procedure should point to an investigation requirement that tracks and trends all failures similar in nature to further identify root cause so that appropriate corrective and preventive measures are applied rather than just repeating the cleaning until all acceptance criteria are met [4]. These deviations are investigated to assess the probable causes and corrections to bring the cleaning process back to a state of control. Preventive maintenance and calibration programs keep equipment and instruments operating correctly and in a calibrated state.

4.2 **Documentation**

The effective management of documentation is essential to comply with GMPs. There are business, regulatory, and scientific reasons to have good control of documents. Good documentation practices ensure traceability of the development, qualification, and maintenance of cleaning processes and enables the company to capture and manage knowledge.

FDA [5] defines validation as:

“The collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.”

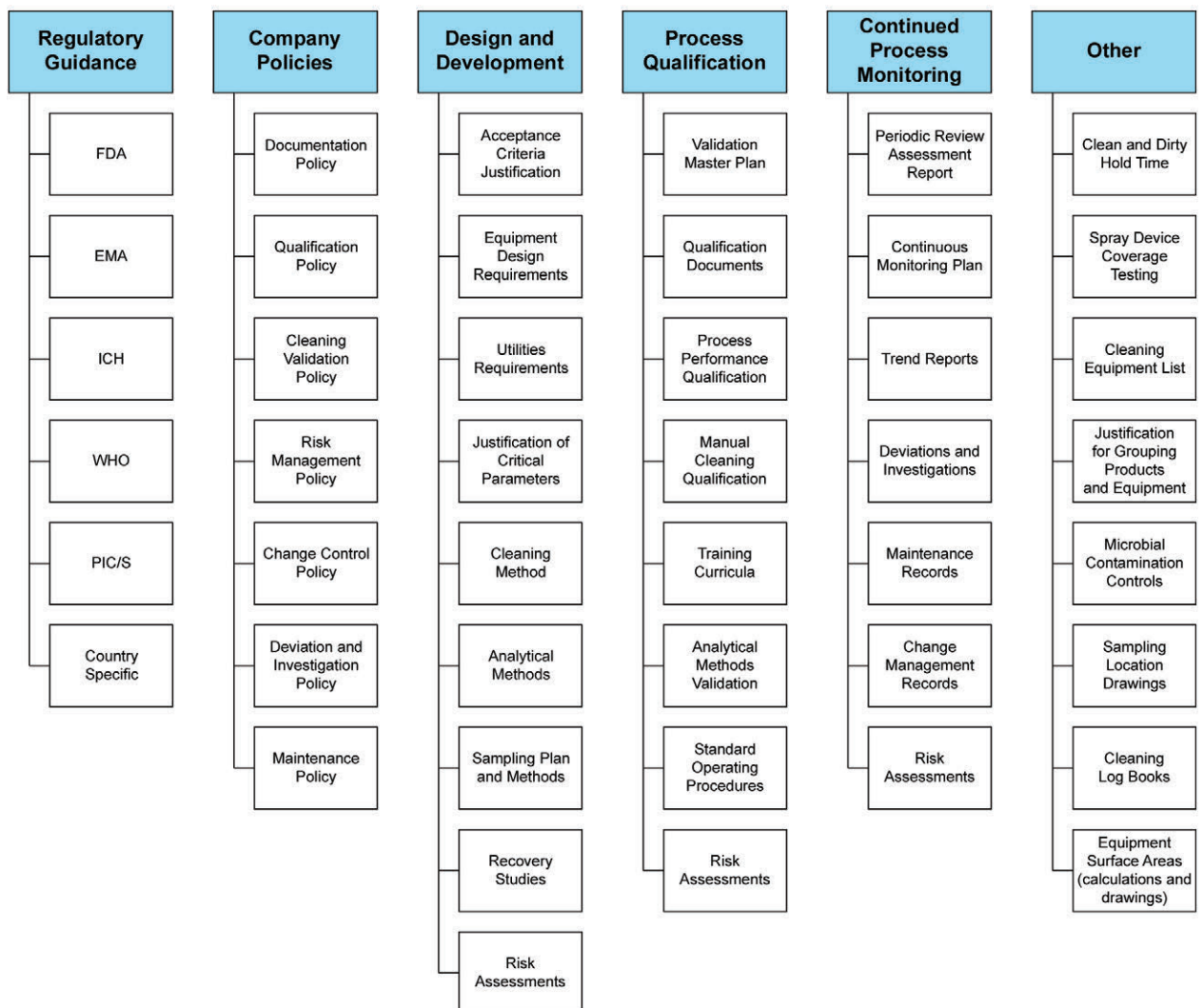
PIC/S [47] and EudraLex Annex 15 [4] define cleaning validation as:

“Documented evidence that an approved cleaning procedure will reproducibly remove the previous product or cleaning agents used in the equipment below the scientifically set maximum allowable carryover level.”

In all the definitions cited above, it is essential to validation to document evidence and collect data accurately, preserve its integrity, and evaluate it to demonstrate that a cleaning process works as intended.

Figure 4.2 describes typical documents associated with developing, qualifying, and maintaining cleaning processes and controls. In general, there is a hierarchy for documentation that starts with company policy and regulations, followed by high-level validation plans, validation protocols, SOPs, laboratory studies, and records.

Figure 4.2: Typical Documentation Associated with Cleaning Validation



4.3 The Validation Master Plan

The VMP states the overall philosophy, intentions, and approach used by the facility for planning, designing, organizing, executing, and reporting validation and qualification activities. The plan is updated periodically to ensure it includes the current state of validation.

The general format of a typical VMP addresses the following elements:

- Cover – Identifies the system or facility described in the plan
- Approval – Identifies the document reviewers and approvers
- Introduction
- Description of validation philosophy and approaches (use of family approaches, methods for defining worst-case conditions, lifecycle of validation, etc.)
- Organizational structure
- Roles and responsibilities
- Description of facility
- Description of manufacturing operations
- Description of key validation procedures
- Guidance on setting and justifying acceptance criteria
- List of qualifications (equipment, utilities, components, etc.)
- List of validations (cleaning, process, analytical methods), maintenance procedures
- References – List of references used to develop the VMP, relevant operating procedures, and policies
- Attachments – Other references such as facility layouts
- History – Documentation of revision history of the VMP

A Cleaning Validation Plan (CVP) can be created as a separate document or included in the site VMP. For cleaning validation, the following additional topics are addressed:

- Surfaces to be cleaned (MOC)
- Product or residue attributes (material to be cleaned) including product formulation information and chemical/physical attributes
- Approaches to product grouping (similar products or residues can be grouped to simplify validation approach)
- Approaches for equipment grouping (equipment may be grouped by similar designs, similar functions, or worst case for cleaning)
- Type of cleaning process (manual, automated, or hybrid)

- Residue limits, visual inspections, LOD, LOQ, and worst-case justifications
- Cleaning parameters
- Sampling types and methodologies (swabs, rinse, sampling location justification)
- Frequency of cleaning

4.4 Creation and Execution of Validation Protocols

The correct execution of protocols is crucial for obtaining the data needed to validate processes. The cleaning validation protocols are written after the cleaning process has been developed. Cleaning PPQ execution cannot begin before approving the validation protocol.

The content of the protocol is product and method-specific to ensure that evidence is collected for validation. Protocol content includes:

- Cleaning procedure to be validated
- Products covered by the protocol; any grouping if used
- Description of equipment and equipment surface area
- Residue materials to be removed
- Cleaning and sanitizing materials used
- Number of runs with rationale, and campaign lengths, if applicable (i.e., validation strategy)
- Cleaning parameters and CPPs to be evaluated
- Analytical methods
- Microbiological methods, if applicable
- Sampling plans, including rationale for the selection of specific sites identified for sampling
- Sampling methods
- Acceptance criteria, reference to calculations, if applicable
- Maximum time interval between use and cleaning, or between cleaning and use, if applicable (i.e., DHT, CHT)

Trial or practice runs are recommended (e.g., for new or complex systems) prior to protocol execution to verify that all the elements of the cleaning process have been properly implemented. Trial runs intended to represent commercial manufacture should include all the controls of the cleaning validation program. Protocol deviations can be minimized during execution by ensuring operational readiness. (Refer to Table 4.4 for a summary of points to consider.)

Table 4.4: Points to Consider when Executing Validation Protocols

For Protocol Readiness	For Operational Readiness	Protocol Execution
• Confirm that written procedures (SOPs) detailing the cleaning process are approved • Verify that recovery methods are ready, analytical equipment is qualified, sample storage conditions are defined, and analytical procedures are approved • Verify that protocol is complete (cleaning method, parameters, sampling plan, number of runs, acceptance criteria, roles and responsibilities are defined, etc.) • Confirm that testing scripts are clearly defined and documented • Clarify when cleaning protocol execution will stop collecting samples or data (end point) • Ensure that protocol is approved prior to execution	• Conduct test or dry runs (correct errors in protocol, confirm that all key steps are included) • Ensure that equipment is qualified and available to conduct cleaning validation • Confirm that utilities and their distribution systems are qualified and available for cleaning operations • Verify that relevant instruments are calibrated and ready for use • Verify that materials, chemicals, utensils, etc. are available for use • Confirm that system for discrepancies and issues management is in place • Complete qualification and training for all persons participating in protocol execution • Ensure Quality Control (QC) laboratories are ready to receive samples for analytical testing • Secure personnel support (e.g., weekends, shifts covering 24 h/day) for the duration of the protocol execution • Qualification reports are satisfactory and approved before Performance Qualification (PQ) execution	• Follow good documentation practices (unambiguous date format, write legibly, no empty or blank spaces) • Use indelible ink when documenting on paper • Collect data accurately, contemporaneously • Document unexpected events or observations immediately • Ensure traceability and chain of custody for validation samples • Ensure sensitive samples (e.g., non-stable, with expiry dates) arrive on time to the testing laboratory • Securely save or file executed validation protocols and attachments after protocol execution

Usually multiple successful cleaning process runs are required to generate the data required for validation. The number of runs required to demonstrate reproducibility and consistency of the cleaning process should be justified based on the process variability and risk. When one or more of the multiple runs fail to meet acceptance criteria, an impact assessment to the cleaning PPQ is necessary.

When cleaning process failures occur, an investigation is initiated to determine the root cause. If the root cause for the failure is related (intrinsic) to the cleaning process, completion of the validation PPQ may be impacted. In order to demonstrate process consistency, consecutive batches are manufactured as evidence. An intrinsic process deviation resulting in a failed cleaning acceptance criterion usually requires extension to the validation by an amount dependent on the nature of the failure and the need to prove consistency of the cleaning process. For example, for automated cleaning processes, the consecutiveness of successful runs during validation is expected. However, for manual processes, a validation approach using consecutive runs may give a false assurance of consistency, and would require a more robust approach to demonstrate validation that takes into consideration the variability between operators.

If the deviation and root cause are extrinsic to the cleaning process, then the consecutiveness of cleaning PPQ runs is normally not interrupted. These decisions are made on a case-by-case basis given the large variety of cleaning methods and equipment/product grouping strategies. However, the decisions should follow certain principles illustrated by these questions:

- Is the root cause for the failed cleaning event intrinsic or extrinsic to the cleaning process?
- Were product quality attributes negatively impacted by the failure?
- Can corrections be implemented to avoid recurrence?

Deviations to cleaning methods or failure to achieve the cleaning acceptance criteria requires investigation according to established deviation procedures. Root cause for the failures and corrective actions are then identified and implemented prior to starting additional cleaning PPQ runs.

All documents created for protocol execution are managed under GMP using the documentation management system of record.

4.5 Periodic Reviews

A Periodic Review (PR) of the cleaning validation process is performed as part of the cleaning lifecycle. The comprehensive review includes multiple data sources relevant to cleaning method control. The frequency of the PR is determined by a risk assessment taking into consideration how frequently the cleaning process is executed, the failure rate for cleaning, and the impact a cleaning failure can have on the company or product supply. The review is conducted formally by SMEs and overseen by the quality unit. All data collected, assessments made, and recommendations are captured in a PR report.

A typical PR report consists of the following:

- Cleaning Process Description
- Scope of the review
 - History of cleaning process changes
 - Evaluation of cumulative impact of changes
 - Summary of critical parameters monitoring
 - Summary of alarms of critical parameters or events
 - Results of routine monitoring
 - Review of non-routine maintenance and events
 - Review of deviations and corrective actions, including visual inspection failures and trends
 - Review of frequencies of recleaning cycles and justification
 - Review of changes to analytical methods
 - Review of equipment inspections and maintenance (scratches, rouging, damages, leaks, etc.)

- Review of data trends
 - Review of risk assessments supporting cleaning validation
 - Review of Cleaning Process Risk Assessment
 - Review of SOP changes and training conducted during this period
 - Evaluation of changes in regulations impacting the cleaning process
- Analysis of the data collected (per scope) and criteria to determine if process is in control
 - Conclusion of the review and recommendations

A robust monitoring program should provide sufficient assurance that a cleaning process is operating in a continuous validated state. However, the monitoring seldom challenges key validation requirements such as sample location, deviations, or the impact of a new product introduction to a facility. For this reason, a comprehensive PR process is recommended to ensure all key elements of the cleaning process are still adequate and in control.

4.6 Cleaning Revalidation

The decision to revalidate a cleaning process usually is taken in the context of changes introduced to the system. (Refer to Chapter 11 for details on change control.) Significant changes impacting cleaning parameters, analytical methods, new technology, or the ability to execute the process may require revalidation. However, not all triggers for revalidation come from individual changes managed via the change control system. The PR process can assess holistically all the elements used to control the cleaning process during a long period of time (usually years) and determine if it is still operating in a validated state or if there are shifts from its expected performance. The extent of the revalidation scope can be limited to certain aspects of the cleaning process (e.g., verification of cleaning hold times), based on the PR assessment.

5 Cleaning Methodologies

5.1 Selection of Cleaning Process

The cleaning process must reduce residues to levels that ensure patient safety and result in visibly clean equipment. An effective cleaning process can reduce equipment downtime, increase the lifetime of the equipment, and minimize the risk of cross-contamination in multiproduct facilities. The objective of development should be a cleaning process that is rugged enough to clean the worst-case soil to levels well below the cleaning limit. The cleaning process should also be rugged enough so that when new products and chemicals, and their resulting residues are introduced into the facility, the existing cleaning process is effective, thus eliminating the need to develop additional cleaning processes and the resulting cleaning validations.

Many factors should be considered during the development of a cleaning process, most importantly, what cleaning method to choose. Cleaning methods are broadly divided into three groups:

- CIP applications – Section 5.2
- COP applications – Section 5.3
- Manual cleaning – Section 5.4

Manual cleaning may be selected for cleaning small parts, parts with small lumens, and delicate parts such as pressure gauges. It involves either wiping the equipment down, cleaning at the sink with a brush, using soaking tanks, or using ultrasonic baths. Manual cleaning is relatively simple; however, it may be inconsistent due to operator-to-operator variability and may be labor intensive if a large number of parts are cleaned in this manner. Small parts such as gaskets, small stainless parts, filter housings, glassware, and carboys are well suited for cleaning using automated parts washers. The advantage of parts washers over manual cleaning is having reliable performance, reduced labor, and no operator exposure to cleaning agents. Large equipment may be cleaned in place or out of place using automated CIP systems or manual methods such as pressure spray, foaming, brushes, or wiping. Cleaning method choice may be restricted due to constraints in building utilities such as the availability of hot water, drains in the area, and mechanical air.

Four key factors needed for reproducible, validatable cleaning are frequently referred to by the acronym TACT (Time, Action, Chemical, and Temperature).

Time – A reproducible cleaning process requires the same duration each time it occurs with regard to phases such as rinses, chemical solution wash, and draining. The criticality of processing times should be evaluated during process development and validated against the target for cleaning validation.

Action – A reproducible cleaning process requires the same surface action each time it occurs. The flow rate/pressure can be quantified within a reasonable range, such that the greatest and least flow rate/pressure are evaluated during development studies and validated at the designed flow rate/pressure. During manual cleaning, action is the type of force on the surface ranging from soaking to agitated immersion or the mechanical action of brushing or wiping.

Chemical – Cleaning agents must be selected for efficacy. The reproducible rate kinetics of cleaning chemicals are affected by concentration. Chemical concentration can be qualified by solution concentration formulation and verified by solution conductivity and/or pH when those analytical characteristics are active to the particular detergent chemical. The chemical concentration can be quantified within a reasonable range, such that the greatest and least concentration conditions are evaluated during coupon development studies and validated at the designed detergent concentration.

Temperature – The reproducible rate kinetics of cleaning agents can be affected by temperature. A reproducible cleaning process requires the same temperature each time it occurs. The temperature can be qualified within a reasonable range during coupon studies, such that the highest and lowest temperature conditions are evaluated and validated at the designated operating temperature.

A rugged cleaning process is directly impacted by the amount of cleaning action on the surface of the equipment [48]. CIP systems rely on a combination of spray impingement, cascading flow, and agitated immersion for cleaning whereas manual cleaning generally exerts more scrubbing action on the surface. Selection of the method should take into consideration the size and quantity of the equipment, design of the equipment, and the level of automation available at the facility.

Development of a Cleaning Process

Development of a cleaning process should include a review and risk assessment of residue characteristics. Review the process development or historical cleaning data, if information is available, to determine the physicochemical characteristics of the residue. Information may also be leveraged from products having similar characteristics or the same products having different cleaning methods.

Consideration should be given to the API; however, in some cases, the API will not be the hardest-to-clean active or the most prolific component in the formulation. For that reason, a thorough review should include any raw materials, excipients, impurities, degradants, or by-products that may contribute to a harder to clean or more toxic residue. The API should be assessed by reviewing pharmacological (represented by the ADE/PDE/HBEL as available) and solubility data, along with its strength or percentage in the formulation.

Review and understand the manufacturing process including processing temperatures, process hold times, and environmental temperatures to understand how these may impact the residue characteristics. Soil condition on the equipment and MOC function together and should be considered when developing the cleaning process. The amount of soil on the equipment should be consistent among batches to ensure consistently adequate cleaning. Depending on the equipment, this can be accomplished using a clean-out step at the end of manufacturing. Scraping and/or vacuuming the equipment can remove the majority of the soil. This serves two purposes: providing a consistent soil level for cleaning and reducing the amount of soil flushed down the drain into the wastewater treatment facility.

Develop an equipment matrix to understand grouping, design, and product contact MOC.

Determine available cleaning process options since there may be limitations with utilities, waste requirements, and automation. Review and understand any restrictions that may influence the cleaning method.

- pH restrictions due to MOC or waste stream limitations
- Temperature restrictions due to MOC or waste stream limitations
- Decontamination step that may change the characteristic of the residue
- DHT constraints

Additional considerations for cleaning process development include: contribution to microbial growth, equipment availability, and manufacturing schedule needs.